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(54) Title: MODULATION OF INTRACELLULAR CALCIUM CONCENTRATION USING NON-EXCITATORY ELECTRICAL SIGNALS APPLIED TO THE TISSUE

(57) Abstract: According to a method and device for modulating intracellular calcium concentration in biological tissue, a stimulation probe is applied to the tissue, a non-excitatory stimulation pulse is generated, and the pulse is conveyed to the stimulation probe. In one embodiment concerning cardiac tissue, a stimulation probe is applied to a patient's heart, a signal is received from at least one sensor responsive to the patient's cardiac muscle activity, a non-excitatory stimulation pulse responsive to the signal is generated, and the pulse is conveyed to the stimulation probe.

MODULATION OF INTRACELLULAR CALCIUM CONCENTRATION USING NON-EXCITATORY ELECTRICAL SIGNALS APPLIED TO THE TISSUE

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/157,511, filed October 4, 1999, which is assigned to the assignee of the present patent application and is incorporated herein by reference.

FIELD OF THE INVENTION

This invention relates generally to invasive devices and methods for treatment of the heart, including devices and methods for stimulation of the heart muscle. More particularly, this invention relates to control of cellular tissue, specifically the modulation of intracellular calcium concentration in cardiac muscle cells.

BACKGROUND OF THE INVENTION

Cardiac insufficiency, characterized *inter alia* by a reduction in cardiac output, is a common, well-known and well-documented heart malfunction. It develops as a result of congenital defects or as an end-effect of many diseases. Cardiac output, i.e., the output of the heart per unit time, is the product of stroke volume and heart rate. Hence, variations in cardiac output can be produced by changes in cardiac rate or stroke volume. The stroke volume can be influenced, for example, by changing the strength of cardiac contraction, by changing the length of the cardiac muscle fibers, and by changing contractility of cardiac muscle independent of fiber length. The heart rate and rhythm influence the cardiac output both directly and indirectly, since changes in the rate and rhythm also affect myocardial contractility.

The human body normally regulates the cardiac output in response to body needs by changing the heart rate, as during physical exercise, and/or by adapting the stroke volume. Under pathological conditions, however, some of the normal regulatory mechanisms may be damaged. For example, heart tissue damaged due to myocardial infarct typically cannot sustain normal pumping function, leading to a reduction in

stroke volume, and hence of cardiac output. The body may react to such a reduction by increasing the heart rate, thus imposing long term strain on the heart muscles, leading in more severe cases to heart failure. There is thus a need for devices and treatments that can regulate the cardiac output, so as to compensate for the deficiencies in the normal regulation mechanisms.

In response to this need, modern cardiology has developed means to control various parameters associated with the heart's operation. Pharmaceuticals, for example, may be used to influence the conduction velocity, excitability, contractility and duration of the refractory period of the heart tissue. These pharmaceuticals are used to treat arrhythmia, enhance cardiac output and prevent fibrillation. Pharmaceuticals are generally limited in effectiveness in that they affect both healthy and diseased segments of the heart, usually, with a relatively low precision. They frequently also have unwanted side-effects.

A special kind of control can be achieved using implantable electronic devices, which provide excitatory electrical stimulation to the heart to control directly the heart rate and/or rhythm. For example, a pacemaker, an electronic device which is typically implanted in the heart to support the heart's electrical excitation system or to bypass a blocked portion of the conduction system. Another type of cardiac electronic device is a defibrillator, which senses fibrillation in the heart and applies a high voltage impulse to "reset" the heart. While electronic pacemakers can control the heart rate, however, they are limited in their capacity to enhance cardiac output, and they are known to reduce stroke volume in at least some instances. Defibrillators are useful in treating arrhythmia when it occurs (although they are painful to the patient and traumatic to the heart), but they provide no long-term amelioration of cardiac insufficiency.

Thus, none of the treatments known in the art allow effective, long-term regulation of cardiac output. PCT patent application PCT/IL97/00012, published as WO 97/25098, to Ben-Haim et al., which is incorporated herein by reference, describes methods for modifying the force of contraction of at least a portion a heart chamber by applying a non-excitatory electric field to the heart at a delay after electrical activation

of the portion. The non-excitatory field is such as does not induce new activation potentials in cardiac muscle cells, but rather modifies the cells' response to the activation.

OBJECTS OF THE INVENTION

It is an object of some aspects of the present invention to provide improved methods and apparatus for controlling calcium concentration in biological tissue.

It is also an object of the present invention to provide methods and apparatus for modulating intracellular calcium concentration in cardiac tissue.

It is a further object of the present invention to provide methods and apparatus for modulating cardiac contractibility.

These and other objects of the invention will become more apparent form the discussion below.

SUMMARY OF THE INVENTION

In preferred embodiments of the present invention, a controller comprises a non-excitatory stimulation probe, including one or more non-excitatory stimulation electrodes, at least one sensor, preferably a sensing electrode; and electronic control circuitry, coupled to the stimulation probe and sensor. The stimulation electrodes and, preferably, the sensor are implemented in the heart. Alternatively, a sensing electrode may be placed on a body surface. The circuitry receives signals from the sensor, indicative of the heart's activity, and responsive thereto, drives the stimulation electrodes to provide non-excitatory electrical stimulation to the heart. A non-excitatory electrical field, current or voltage is passed through biological tissue, such as cardiac tissue, or in its proximity, resulting in either changing trans-membranal calcium ion fluxes or and/or intracellular stores content.

The term "non-excitatory electrical stimulation" ("IDS") in the context of the present patent application and in the claims, refers to electrical pulses that do not induce new activation potentials to propagate in cardiac muscle cells. Rather, such pulses

generally affect the response of the heart muscle to the action potentials, possibly by modulating cell contractility within selected segments of the cardiac muscle.

In any case, the effect of the device on intracellular calcium concentration is preferably regulated by changing the timing of the non-excitatory stimulation pulse relative to the heart's activity, preferably relative to the heart's local electrical activity or ECG signals received by the sensing electrode, and/or by changing other pulse characteristics, such as voltage, current, duration, polarity, waveform and frequency of the waveform. Preferably, the device senses the heart's sinus rhythm and applies and synchronizes the stimulation pulse relative thereto, preferably with a delay before the onset of the stimulation pulse. Additionally, the circuitry may analyze the signals, for example, to determine the QT interval, so as to adjust the stimulation pulses responsive thereto. Alternatively, when the heart's rhythm is irregular, due to ventricular premature beats (VPB's) or other cardiac arrhythmias, the device preferably identifies and analyzes the irregularity, using signal processing methods known in the art, and adjusts or withholds the stimulation pulse accordingly.

In some preferred embodiments of the present invention the control circuitry is contained within a console external to the body, and the electrodes are fed percutaneously into the subject's vascular system, for example, through the femoral artery, and are implanted in the heart. Such embodiments are useful particularly in short-term therapy to regulate and stabilize the subject's hemodynamics following an insult or trauma, for example, open heart surgery or MI.

In alternative preferred embodiments of the present invention, the electronic control circuitry is contained within a miniaturized, implantable case, similar to pacemaker cases known in the art.

In some preferred embodiments of the present invention, the non-excitatory stimulation electrodes known in the art, such as pacing or electrophysiology electrodes. Preferably, the stimulation electrodes comprise large-area carbon electrodes or any other metal electrodes such as titanium nitrate, iridium oxide, most preferably vitreous carbon, or alternatively, pyro-carbon. Both types of carbon materials are known for their

compatibility with heart tissue, in-vivo durability and excellent electrical properties, including high electrical conductivity. Thus, they allow a relatively high electrical current to be delivered to a relatively large segment of the heart tissue, without inducing electrical excitation.

In other preferred embodiments of the present invention, the non-excitatory stimulation electrodes are inserted into one of the blood vessels of the heart, preferably into the coronary sinus, or alternatively, into a coronary artery.

In another preferred embodiment of this type, different stimulation pulses are applied to respective ones or groups of the plurality of stimulation electrodes. Preferably, the different stimulation pulses are applied to the respective electrodes with a predetermined delay between the different pulses. The delay may be varied so as to achieve a desired hemodynamic effect, for example, to maximize the increase in stroke volume.

In still other such preferred embodiments, the positions of the plurality of stimulation electrodes and/or characteristics of the stimulation pulses applied thereto are optimized responsive to clinical characteristics of the heart. Preferably, before insertion of the electrodes, a map of the heart is produced, for example, an electrophysiological map, as described in U.S. Patent 5,568,809, or a phase-dependent geometrical map, as described in PCT Patent Application PCT/IL97/00011, both of which are incorporated herein by reference. Preferably, the map includes information regarding the viability of the heart tissue, for example, based on local contractility or electrical activity. The non-excitatory stimulation electrodes are then positioned responsive to the map.

Preferably, applying the IDS signal includes conveying electrical energy to cells of the heart, such that action potentials are generally not generated in the cells responsive to the application of the non-excitatory signal.

Further preferably, the IDS signal is applied to improve hemodynamic performance of the heart. Preferably, the IDS signal is applied in order to increase contractility of the heart or, alternatively or additionally, to increase systolic pressure generated by the heart.

In a preferred embodiment, applying the IDS signal includes sensing physiological variables and applying the signal responsive thereto. Preferably, sensing the variable includes detecting an electrical depolarization wave in the tissue. Alternatively, sensing the variable includes sensing a hemodynamic parameter. Preferably, applying the pacing pulses include controlling application of the pacing pulses responsive to the variable, wherein controlling the application of the pacing pulses includes making a transition from a first stimulation mode to a second stimulation mode responsive to the variable.

There is also provided, in accordance with a preferred embodiment of the present invention, apparatus for stimulating cardiac tissue, including:

a plurality of electrodes, which are placed at multiple sites in at least two different chambers of the heart; and

an electrical control unit, which applies pacing pulses to two or more of the electrodes at respective pacing sites in the at least two different chambers, and which applies an IDS signal to at least one of the electrodes in a vicinity of one or more of the pacing sites following application of the pacing pulse at the site.

Preferably, the at least one of the electrodes to which the IDS signal is applied includes one of the electrodes to which the pacing pulses are applied.

Further preferably, at least one of the pacing sites is in the left ventricle, and the IDS signal is applied to an electrode in the left ventricle.

Preferably, the control unit applies the IDS signal between during a time period which begins between about 0 and 100 ms after the onset of a pacing pulse applied by the control unit, wherein the time period is set so as to substantially eliminate the possibility that a propagating action potential will be generated responsive to application of the IDS signal. Preferably, the time period begins between about 10 and 50 ms after the onset of the pacing pulse.

Preferably, the IDS signal is applied in order to increase contractility of the heart or, alternatively or additionally, in order to increase systolic pressure generated by the heart.

In a preferred embodiment, the apparatus includes a sensor, which senses a physiological variable, wherein the control unit receives an input from the sensor and applies the IDS signal responsive thereto. Preferably, the sensor detects an electrical depolarization wave in the tissue. Alternatively (or additionally, the sensor senses a hemodynamic: parameter or senses motion. Preferably, the control unit controls application of the pacing pulses responsive to the variable. Further preferably the control unit makes a transition from a first stimulation mode to a second stimulation mode responsive to the variable.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be more fully understood form the following detailed description of the preferred embodiments thereof, taken together with the drawings, in which:

Fig. 1A is a graph of shortening vs. time, before, during, and after an IDS signal;

Fig. 1B is a graph of calcium concentration vs. time;

Fig. 2A is a graph of calcium concentration vs. time;

Fig. 2B is a graph of shortening vs. time;

Fig. 3 depicts two graphs vs. time, graph (a) representing concentration form vs. time, and graph (b) represents action potential vs. time; and

Fig. 4 depicts two graphs of concentration force vs. time, (a) being a control and (b) representing the use of a drug.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

This invention is designed to modulate intracellular calcium concentration in a biological tissue using a non-excitatory electrical signal (IDS). In particular, the

invention relates to the modulation of the intracellular calcium in cardiac muscle cells and thus the modulation of cardiac contractility. According to this invention a non-excitatory electrical field, current or voltage is passed through the tissue or in its proximity, resulting in either changing trans-membranal calcium ion fluxes or an intracellular calcium stores content. In another aspect of the invention the electrical field may interfere/enhance the affinity of intracellular calcium binding elements to calcium. In a further aspect the rise in intracellular calcium concentrations may initiate a cascade of events including, but not limited to, phosphorylation/dephosphorylation, gene transcription, and/or post translation modification.

Systems are disclosed which utilize the application of electrical current to a tissue, effecting tissue contractility by means of modulating intracellular calcium. At least one pair of electrodes is used for applying the signal. Electrode placement is adapted for achieving the maximum desired effect. The electrodes are attached to an either implantable or external device with programming capabilities. This device can be tested and calibrated non-invasively by external mechanisms. In addition, stimulation parameters can be adjusted by a similar programming mechanism.

The characteristics of the electrodes used for the stimulation are important. This invention utilizes both uni-polar and bi-polar electrode configurations.

A novel aspect of this method of modulating intracellular calcium in cells is the ability to adjust the timing and the amount of calcium increase/decrease using temporal electrical current rather than systemic pharmacological agents.

The accompanying figures show changes in intracellular calcium resulting from the application of the IDS signal together with experimental evidence on the effect of the IDS signal on the calcium handling in the cell. Figure 1A represents the shortening of a single isolated myocyte measured using optical means. Each of the lines represents a single contraction of the myocyte. When the IDS signal was delivered, a marked increase in the myocyte shortening of 30.9 $\pm$5% (n=10) was observed. The shortening returned to baseline when signal delivery was stopped.

Figure 1B shows the optical measurements of calcium concentration from a single myocyte without the application of the IDS signal (dark line) and on top of it superimposed the intracellular calcium concentration during the delivery of the IDS signal (gray line). An increase of 26.6% (n=3) in the peak calcium level was observed. The calcium concentration changes were measured using the florescence ration of a calcium sensitive dye Fura-2 at two wavelengths, 340 nm and 380 nm. The same result showing a large increase in calcium concentration was measured from an isolated ferret heart using a Langendorf setting. The ventricle contraction force and contractility increased by up to 50%, and at the same time cellular calcium concentration, measured using Aquarine calcium sensitive dye, was increased by up to 50%.

Figures 2A and 2B show the effect of the IDS signal on the shortening and intracellular calcium of myocytes isolated from canine heart with heart failure (generated by repeated ischemia events). Each line represents an average of 20 consecutive beats before (black line) and during (gray line) the application of the signal. Figure 2A shows an increase of 24.9 $\pm$ 3.9% (n=-11) in shortening. Figure 2B shows an increase of 29.7% (n=3) in intracellular calcium measured using Fluo-3 fluorescence.

Figure 3 depicts initial changes in contraction force and in action potential duration, measured using an intracellular electrode, during the first three beats of IDS signal application to a rabbit papillary muscle. The action potential duration when the IDS signal is applied (gray line in the lower trace) is superimposed on a control contraction (black line in the middle trace). Black lines, in the upper trace, mark the start of application of the IDS signal. The action potential duration immediately changes upon the application of the IDS signal from the first pulse. There is no significant difference between action potential duration in the consecutive beats. The contraction force behaves differently; there is a small increase in the contraction force on the first beat followed by a larger increase in the second beat and gradual changes until a plateau is reached after 5 to 6 beats. The underlying mechanism is that the IDS signal prolongs action potential duration. As a result of action potential prolongation the flow of calcium into the cell increases and generates two effects:

(1) immediate increase in the Sarcolemal calcium level causing the initial increase in the contraction force on the first beat; and

(2) increase in the stored calcium in the Sarcoplasmatic Reticulum (SR) that is released during the following contractions and induces a larger increase in contraction until a new steady state is reached with higher contraction force.

The initial increase in the contractile force also supports the possible increase in the affinity of intracellular calcium binding elements that cause part of the increase in the contraction force.

Figure 4 provides additional evidence supporting the hypothesis of calcium entry. The lower trace shows the increase in contraction force of a rabbit papillary muscle as a result of an IDS signal (shown as a black line on the upper trace). The initial increase in contraction on the first beat followed by the gradual change in the following beats is clearly seen. The middle trace shows the change in contraction force of the same muscle after the addition of the Ryanodine to the bath solution. Ryanodine prevents the accumulation of calcium in the Sarcoplasmatic Reticulum and therefore decreases the baseline contraction force. Upon the application of the IDS signal the contraction force increases immediately on the first beat, but no increase occurs during the following beats since the SR mechanism is disabled by the Ryanodine and no accumulation of calcium in the SR can contribute to the additional increase in contraction force exist.

All such variations, applications and subcombinations of elements are considered to be within scope of the present invention. It will thus be appreciated that the preferred embodiments described above are cited by way of example, and the full scope of the invention is limited only by the claims.

WE CLAIM:

1. A method of modulating intracellular calcium concentration in biological tissue, which comprises the steps of:

(a) applying a stimulation probe to biological tissue;

(b) generating a non-excitatory stimulation pulse; and

(c) conveying the pulse to the stimulation probe.

2. The method of Claim 1, wherein the stimulation probe comprises one or more stimulation probes.

3. The method of Claim 1, wherein the intracellular calcium concentration is increased.

4. The method of Claim 1, wherein the intracellular calcium concentration is decreased.

5. A method of modulating intracellular calcium concentration in cardiac tissue, comprising:

(a) applying a stimulation probe comprising one or more stimulation electrodes to a subject's heart;

(b) receiving a signal from at least one sensor responsive to the subject's cardiac muscle activity;

(c) generating a non-excitatory stimulation pulse responsive to the signal; and

(d) conveying the pulse to at least one of the one or more electrodes.

6. The method of Claim 5, wherein the intracellular calcium concentration is increased.

7. The method of Claim 5, wherein the intracellular calcium concentration is decreased.

8. The method of Claim 5, wherein receiving the signal comprises introducing a sensing electrode into the heart and receiving signals therefrom, and wherein generating the stimulation pulse comprises generating a pulse synchronized with electrical activity sensed by the sensing electrode.

9. The method of Claim 5, wherein receiving the signal comprises applying an electrode to a body surface and receiving signals therefrom, and wherein generating the stimulation pulse comprises generating a pulse synchronized with an ECG signal.

10. The method of Claim 5, wherein receiving the signal comprises receiving signals from at least one of the one or more stimulation electrodes.

11. The method of Claim 5, wherein generating the stimulation pulse comprises generating a pulse having a predetermined delay relative to the signal.

12. The method of Claim 5, wherein applying the stimulation probe comprises applying a probe comprising a plurality of stimulation electrodes, and wherein generating and conveying the pulse comprises generating a sequence of pulses and applying each pulse in the sequence to a different one of the plurality of stimulation electrodes.

13. The method of Claim 5, wherein generating and conveying the stimulation pulse comprises generating and conveying stimulation pulses selectively, based on a characteristic of the signals received from the at least one sensor.

14. The method of Claim 13, wherein generating and conveying the pulses comprises generating and applying pulses at a rate dependent on the heart rate, but not equal to the heart rate.

15. The method of Claim 13, wherein generating and conveying the pulses comprises detecting a cardiac arrhythmia and adjusting the application of the pulses responsive thereto.

16. The method of Claim 13, wherein generating and conveying the pulses comprises detecting a QT interval in the signals and generating pulses responsive thereto.

17. The method of Claim 5, wherein generating the non-excitatory stimulation pulse comprises varying one or more parameters of the pulse, selected from the group consisting of the pulse voltage, current, duration, delay, and waveform frequency.

18. The method of Claim 5, wherein the pulse comprises a baseline pulse and a waveform of substantially higher frequency than the baseline pulse superimposed thereon.

19. The method of Claim 18, wherein the waveform comprises a square wave.

20. The method of Claim 5, and comprising, after generating and conveying the non-excitatory stimulation pulse, generating and conveying another pulse of opposite polarity thereto.

21. The method of Claim 5, wherein applying the non-excitatory stimulation pulse comprises varying the extent of a portion of the area of the heart segment to which the stimulation pulse is applied.

22. The method of Claim 21, wherein varying the extent comprises selectively addressing a net of stimulation electrodes implanted in the heart.

23. The method of Claim 5, wherein applying the stimulation probe comprises inserting the one or more stimulation electrodes into multiple chambers of the heart.

24. The method of Claim 5, wherein implanting the stimulation probe comprises inserting at least one of the one or more stimulation electrodes into a blood vessel of the heart.

25. The method of Claim 24, wherein inserting the at least one stimulation electrode comprises inserting the electrode into the coronary sinus.

26. The method of Claim 5, wherein generating and conveying the pulse comprises generating and conveying pulses at selected times of day.

27. The method of Claim 5, wherein generating and conveying the pulses comprises generating and conveying pulses which increase the subject's cardiac output.

28. The method of Claim 5, wherein generating and conveying the pulses comprises generating and conveying pulses which decrease the subject's cardiac output.

29. The method of Claim 5, wherein generating and conveying the pulses comprises generating and conveying pulses which increase the efficiency of contraction of the heart.

30. An apparatus for modulating intracellular calcium concentration in biological tissue, comprising:

a stimulation probe, and

an electrical control unit capable of generating a non-excitatory stimulation pulse and conveying said pulse to the stimulation probe to modulate intracellular calcium concentration.

31. The apparatus of Claim 30, wherein the stimulation probe comprises one or more stimulation electrodes and the pulse is conveyed to one or more of said stimulation electrodes.

32. The apparatus of Claim 30, wherein the intracellular calcium concentration is increased.

33. The apparatus of Claim 30, wherein the intracellular calcium concentration is decreased.

34. An apparatus for modulating intracellular calcium concentration in cardiac tissue, comprising:

a stimulation probe comprising one or more stimulation electrodes,

at least one sensor capable of generating a signal responsive to cardiac activity, and

an electrical control unit capable of generating a non-excitatory stimulation pulse responsive to the signal and conveying said pulse to at least one or the one or more stimulation electrodes to modulate intracellular calcium concentration.

35. The apparatus of Claim 34, wherein the intracellular calcium concentration is increased.

36. The apparatus of Claim 34, wherein the intracellular calcium concentration is decreased.

37. The apparatus of Claim 34, which also comprises a sensing electrode to be introduced into the heart to sense signals and the stimulation pulse is synchronized with electrical activity sensed by the sensing electrode.

38. The apparatus of Claim 34, wherein the stimulation pulse is synchronized with an ECG signal from an electrode applied to a body surface.

39. The apparatus of Claim 34, wherein signals are received from at least one of the one or more stimulation electrodes.

40. The apparatus of Claim 34, wherein the stimulation pulse generated has a predetermined delay relative to the signal.

41. The apparatus of Claim 34, wherein the stimulation probe comprises a plurality of stimulation electrodes, and wherein the electrical control unit generates a sequence of pulses and applies each pulse in the sequence to a different one of the plurality of stimulation electrodes.

42. The apparatus of Claim 34, wherein the electrical control unit generates and conveys stimulation pulses selectively, based on a characteristic of the signals received from the at least one sensor.

43. The apparatus of Claim 42, wherein the electrical control unit generates and applies pulses at a rate dependent on the heart rate, but not equal to the heart rate.

44. The apparatus of Claim 42, wherein the electrical control unit detects a cardiac arrhythmia and adjusts the application of the pulses responsive thereto.

45. The apparatus of Claim 42, wherein the electrical control unit detects a QT interval in the signals and generates pulses responsive thereto.

46. The apparatus of Claim 34, wherein in generating the non-excitatory stimulation pulse the electrical control unit varies one or more parameters of the pulse selected from the group consisting of the pulse voltage, current, duration, delay, and waveform frequency.

47. The apparatus of Claim 34, wherein the pulse comprises a baseline pulse and a waveform of substantially higher frequency than the baseline pulse superimposed thereon.

48. The apparatus of Claim 47, wherein the waveform comprises a square wave.

49. The apparatus of Claim 34, wherein after generating and conveying the non-excitatory stimulation pulse, the electrical control unit generates and conveys another pulse of opposite polarity thereto.

50. The apparatus of Claim 34, wherein the electrical control unit varies the extent of a portion of the area of the heart segment to which the non-excitatory stimulation pulse is applied.

51. The apparatus of Claim 50, wherein varying the extent comprises selectively addressing a net of stimulation electrodes implanted in the heart.

52. The apparatus of Claim 34, wherein the one or more stimulation electrodes as inserted into multiple chambers of the heart.

53. The apparatus of Claim 34, wherein at least one of the one or more stimulation electrodes are inserted into a blood vessel of the heart.

54. The apparatus of Claim 34, wherein at least one stimulation electrode is inserted into the coronary sinus.

55. The apparatus of Claim 34, wherein the electrical control unit generates and conveys pulses at selected times of day.

56. The apparatus of Claim 34, wherein the electrical control unit generates and conveys pulses which increase the subject's cardiac output.

57. The apparatus of Claim 34, wherein the electrical control unit generates and conveys pulses which decrease the subject's cardiac output.

58. The apparatus of Claim 34, wherein the electrical control unit generates and conveys pulses which increase the efficiency of contraction of the heart.

FIG. 1A

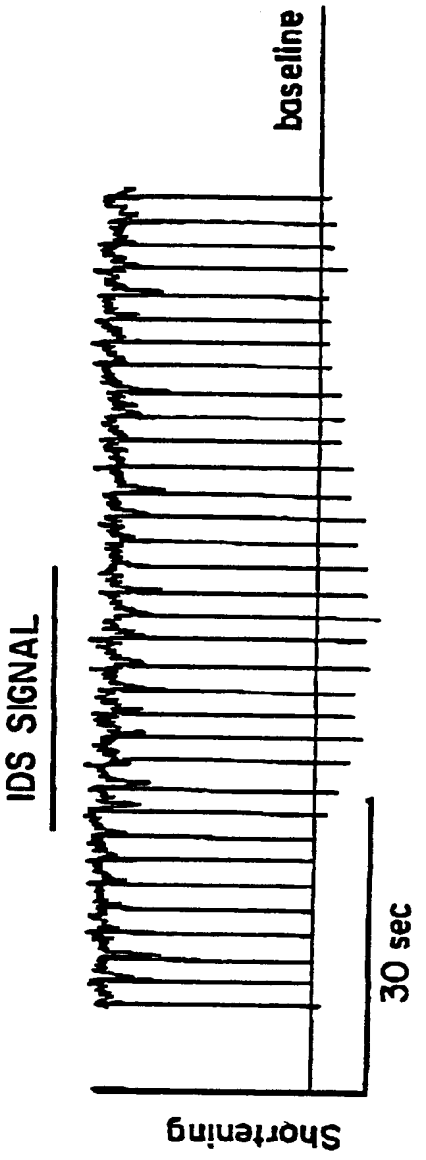


FIG. 1B

FIG. 2A

FIG. 2B

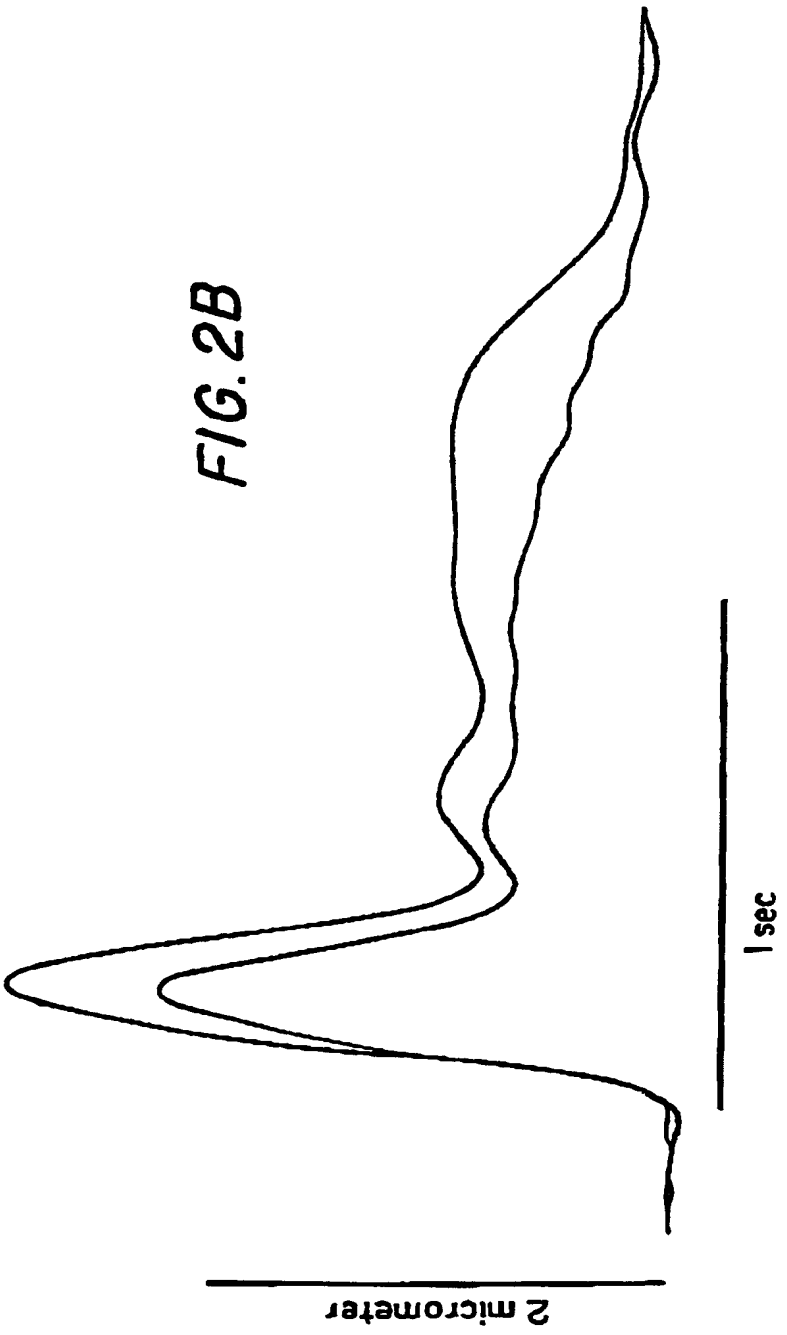


FIG. 3(a)

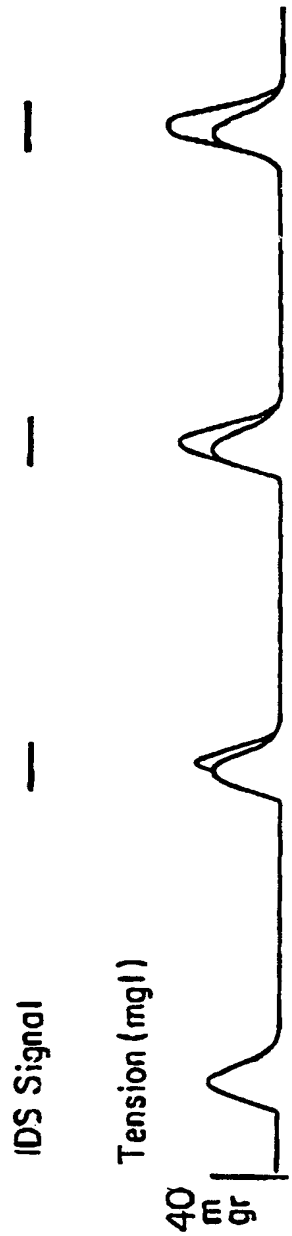


FIG. 3(b)

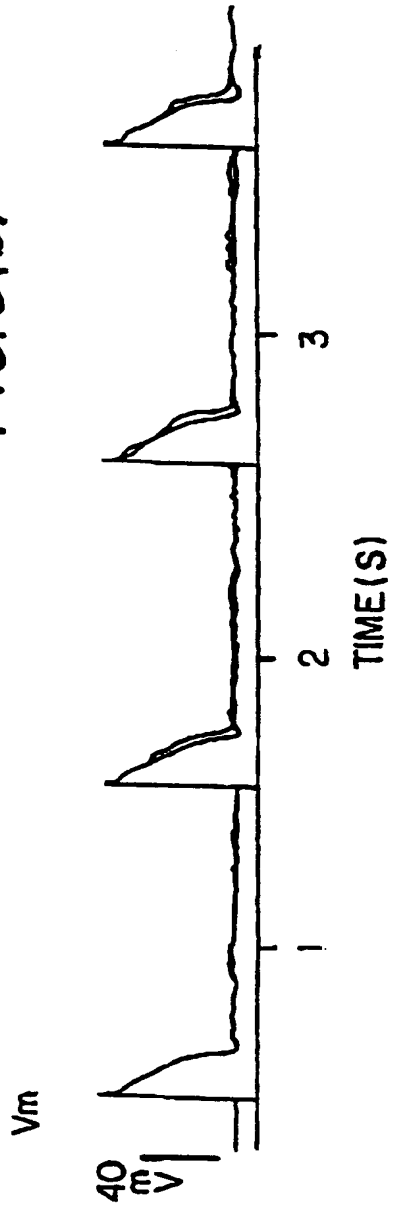
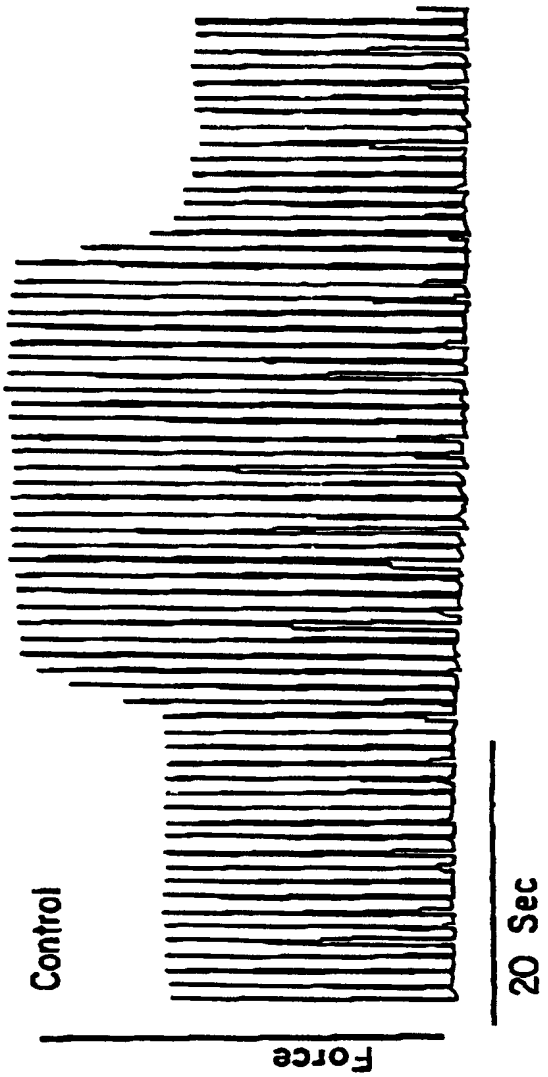


FIG. 4(b)

FIG. 4(a)



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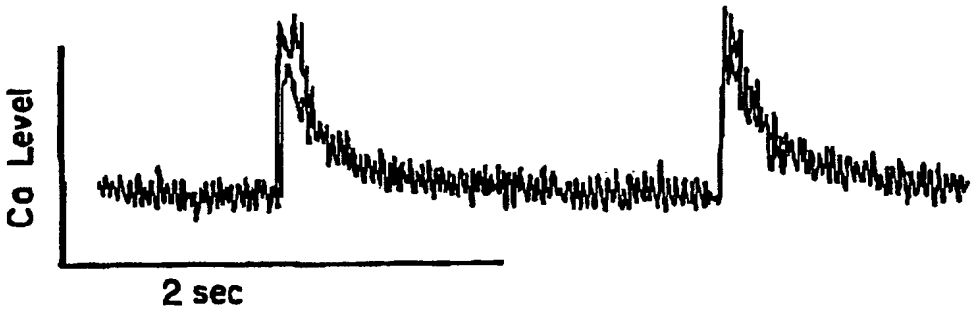
(54) Title: MODULATION OF INTRACELLULAR CALCIUM CONCENTRATION USING NON-EXCITATORY ELECTRICAL SIGNALS APPLIED TO THE TISSUE



(57) Abstract: According to a method and device for modulating intracellular calcium concentration in biological tissue, a stimulation probe is applied to the tissue, a non-excitatory stimulation pulse is generated, and the pulse is conveyed to the stimulation probe. In one embodiment concerning cardiac tissue, a stimulation probe is applied to a patient's heart, a signal is received from at least one sensor responsive to the patient's cardiac muscle activity, a non-excitatory stimulation pulse responsive to the signal is generated, and the pulse is conveyed to the stimulation probe.

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INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61N 1/18
US CL :607/9
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 607/9, 22, 62; 600/308, 309, 345, 358, 554; 422/82.05

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	US 5,871,506 A (MOWER) 16 February 1999. See entire document and column 7 line 61 to column 8 line 4 in particular .	1-4, 30-33 ---- 5-29 and 34-58
X,P --- Y	US 6,136,019 A (MOWER) 24 October 2000. See entire document	1-4, 30-33 ---- 5-29, 34-58
X, P --- Y,	US 6,141,587 A (MOWER) 31 October 2000. See entire document	1-4, 30-33 ---- 5-29 and 34-58
X	US 5,320,642 A (SCHERLAG) 14 June 1994. See entire document noting the use of subthreshold stimulation as the A-V junction.	1-4, 30-33

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

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INTERNATIONAL SEARCH REPORT

International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,320,643 A (ROLINE et al.) 14 June 1994. See entire document including threshold detection means for adjusting stimulation.	5-29, 34-58